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<p>(54) Title: IN VIVO BLOOD TESTING</p>			
<p>(57) Abstract</p> <p>Apparatus is disclosed for sensing blood gas concentration <i>in vivo</i>, which comprises a probe adapted for emplacement in a vein or artery and including: (a) at one end thereof, a gas-permeable membrane formed of a biologically acceptable material; (b) contiguous with said membrane, an active surface in the form of a surface capable of supporting a plasmon resonance; and (c) a light guide of a type capable of transmitting a light input to said active surface and of transmitting a light output away from said active surface, without mutual interference, wherein the light guide constitutes a support or substrate for said active surface and is in optical communication therewith.</p>			

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IN VIVO BLOOD TESTING

This invention relates to in vivo blood gas analysis using Raman spectroscopy.

5 Vibrational spectroscopy has been employed for many years to study the structure and bonding of molecules. As each bond has its own, characteristic frequency, vibrational spectra and molecular structure are related. In this way, compositional analysis can be carried out by inspecting the vibrational spectrum of a
10 sample and comparing it with the spectra of known compounds.

The two main techniques employed are infrared absorption and Raman spectroscopy. In the first case, a wavelength tunable or broadband light source is used to
15 illuminate the specimen, and the wavelengths at which energy is absorbed are recorded. In Raman spectroscopy, a fixed wavelength source is employed, and the spectrum of emitted radiation recorded; the maxima in the emission spectrum represent the difference in energy
20 between the incoming light quanta and the vibrational energy of the molecular bonds in the sample.

In general, vibrational energy levels lie in the infrared, and this represents a disadvantage for infrared absorption spectroscopy. Ideally one requires a tunable
25 or broadband source of IR radiation. Although this is clearly possible using thermal radiation, in general power levels are low, and detectors with the required sensitivity are expensive.

With Raman spectroscopy, however, one can
30 illuminate the sample in the visible waveband, for example using a fixed frequency laser, and generate an emitted spectrum, shifted to the red, representative of the sample composition.

The major disadvantage to Raman scattering is that
35 it is a weak process, relying on a non-linear interaction between the source radiation and the sample. In the past this has meant that even for concentrated samples under

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1 ideal conditions photon counting and photomultiplier tubes have to be employed to detect the emitted radiation. Remote detection, when the sample volume may be small, or dilute, has therefore been impractical.

5 In the technique we propose, a method of compositional analysis utilises the enhancement of the efficiency of generation of the Raman spectrum by using a configuration in which a surface plasmon is excited in an appropriate surface layer and the Raman spectrum is
10 simultaneously generated. It is known that when a surface plasmon is excited, the electric field associated with the electromagnetic wave is highly enhanced (by a factor of 10^3 to 10^4). This means that it will interact with high efficiency with molecules in close proximity to
15 the surface; the excitation efficiency of the Raman spectrum is much higher than would be the case without the surface plasmon phenomenon. In addition, excited molecules in close proximity to a metal surface can radiate light by co-operating with the metal surface;
20 the 'image' of the molecular dipoles acts with the molecules themselves to form a 'phased array' of emitters. This emission can interact with the surface plasmon resonances of the metal surface so that the light is emitted in known, calculable directions. Thus the
25 collection efficiency of the Raman spectrum is enhanced.

The present invention is particularly concerned with a sensor head designed specifically for use in in vivo monitoring of blood gases. The sensor is capable of both identification of gases and continuous measurement of their concentration.
30

In blood gas analysis, one is usually concerned with the measurement of O_2 and CO_2 partial pressures in both arterial and venous flow, although the technique of the present invention may also be applicable to the
35 detection of other analytes. Current techniques are based on either electrochemical (potentiometric or amperometric) or optical sensors. For example, the

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1 Cardiomet 4000 system manufactured by Biomedical Sensors
Limited of High Wycombe, UK combines pO_2 measurement
using an electrochemical sensor based on a Clark
electrode with pCO_2 and pH measurement based on the
5 optical absorption properties of chemical dyes.
Electrochemical sensors suffer from some problems
associated with their complexity and fragility which
makes for example miniaturisation of the sensors
difficult. This is particularly relevant to in vivo
10 blood gas analysis.

There have been recent developments in
electrochemical sensors, such as the use of ion selective
field effect transistors (ISFETS). However the
15 productionisation of such systems has not yet been fully
addressed.

In addition to optical sensors based on absorption
and fluorescence, fibre optic sensors, either extrinsic
or intrinsic, can be developed for application in blood
gas analysis. The problem with such intrinsic sensors is
20 the identification of a transduction mechanism
appropriate to the particular parameter which is to be
sensed.

The present invention utilises a single optical
technique for the monitoring of a number of blood gases
25 e.g. pO_2 and pCO_2 . The technique is also applicable to
the detection and measurement of other blood gas
analytes. Its simplicity compared with electrochemical
sensors and versatility to monitor a plurality of
30 analytes make it an attractive alternative sensor
technology.

The present invention provides a method of
analysis which utilises enhancement of the efficiency of
Raman spectrum generation in a configuration in which a
surface plasmon resonance is generated in an appropriate
35 surface layer and the Raman spectrum is generated
(normally simultaneously with the plasmon excitation).

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1 According to one aspect of the present invention,
there is provided apparatus for sensing blood gas
concentration in vivo, which comprises a probe adapted
for emplacement in a vein or artery and including: (a) at
5 one end thereof, a gas-permeable membrane formed of a
biologically acceptable material; (b) contiguous with
said membrane, an active surface in the form of a surface
capable of supporting a plasmon resonance; and (c) a
light guide of a type capable of transmitting a light
10 input to said active surface and of transmitting a light
output away from said active surface, without mutual
interference, wherein the light guide constitutes a
support or substrate for said active surface and is in
optical communication therewith.

15 Conveniently, the light guide comprises a pair of
parallel optical fibres, one acting as an afferent light
guide and the other as an efferent light guide.

In practice, the gas-permeable membrane will come
into contact with a patient's blood and dissolved gases
20 (O_2 and CO_2) will cross the membrane and contact the
active surface. This is then illuminated by radiation
arriving via the afferent fibre and a plasmon
resonance-enhanced Raman spectrum is collected by the
efferent fibre and directed towards a remotely located
25 spectral detection system.

The active surface can be in the form of a
metal-coated grating or prism surface. Alternatively the
surface may be constituted by a dispersion of small metal
spheres, as will be described in more detail hereinafter.

30 The invention will now be described in more detail
by way of example, with reference to the accompanying
drawings, in which:

FIGURE 1 is a schematic illustration of the
generation of a surface plasmon resonance enhanced Raman
35 spectrum;

FIGURES 2a and 2b illustrate schematically two
embodiments of the active surface used in the invention;

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1 FIGURE 2c illustrates schematically the production
of a Raman spectrum;

FIGURES 3 and 4 are schematic illustrations of two
arrangements in accordance with the invention;

5 FIGURE 5 illustrates an alternative embodiment of
the active surface; and

FIGURES 6 to 9 illustrate four arrangements of a
probe in accordance with the inventions each
incorporating a different active surface/light collecting
10 arrangement.

Referring now to the drawings, the general layout
is as shown in Figure 1. It will be appreciated that
components shown in the drawings are not drawn to scale;
the enlargement of certain items whose dimensions are of
15 the order of the wavelength of light is necessary for
clarity. A sensor head 1 supports an active surface 2
which, in this embodiment, is in the form of a grating.
A source 3 of coherent radiation, e.g. a laser operating
in the visible or near infra-red, produces a collimated
20 beam λ_i which is directed at the active surface 2 at
an angle of incidence θ_i . Surface plasmon enhanced
Raman emission occurs and the emitted rays λ_S are
detected by a detection system 4. The illumination
source and detection systems do not form a part of the
25 present invention. In the presence of a material, e.g. a
specific gas, whose presence is to be detected, the
enhanced Raman emission is affected in a specific and
detectable manner; in this way, the detection and
measurement of the Raman emission is used to give a
30 qualitative and/or quantitative indication of the
presence of the material.

The sensor itself comprises a metal coated
substrate which may be part either of a prism (also known
as Kretschmann or Otto geometry) or of a grating assembly.
35 These arrangements are shown schematically in Figure 2.
As shown in Figure 2c, the metal grating has a dielectric
constant E_M while the dielectric medium onto which the

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1 metal layer is deposited has a dielectric constant ϵ_i .
Surface plasmon generation can occur at the metal
dielectric interface ϵ_i , ϵ_m . The wavelength and angle of
incidence of the illumination source, and the pitch,
5 depth and groove shape of the grating (if used) are
chosen to ensure efficient surface plasmon generation at
the interface. This configuration, in which surface
plasmon and Raman spectrum are generated simultaneously,
provides enhancement of the efficiency of Raman spectrum
10 generation.

In Figure 2a, the sensor head comprises a prism
which carries a metal film 2 on one surface; the film 2
communicates directly with a conduit C through which the
material undergoing analysis is passed. The arrangement
15 of Figure 2b is different in that the active metal film 2
is spaced from the prism by a narrow gap (e.g. of 1
micrometre or less) which forms part of the conduit C.

It is a feature of the in vivo blood gas sensor to
which this invention relates that the sensor head is
20 positioned remote from the illumination source, for
example at the end of a catheter assembly which can be
inserted into the patient's blood flow in a vein or
artery. The illuminating light is transmitted to the
sensor, e.g. via an optical fibre, with the generated
25 Raman spectrum returning to the main instrument via the
same route. A single fibre or two fibres, delivery and
receiver, may be used. This is shown in diagrammatic
form in Figures 3 and 4. In Fig. 3, there is a single
30 optical fibre 5 which conveys light at 6 from the
illumination system (not shown) to the sensor assembly 1
and also conveys the Raman emission at 7 from the sensor
assembly 1 to the detector system (not shown). In Fig.
4, two separate optical fibres are located in a conduit 8
35 and serve to transmit the afferent illumination 6 and the
efferent signal 7.

Particular features of the in vivo sensor head are
described below. Highly efficient surface plasmon

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- 1 generation can occur at a metal-dielectric interface when
the momentum of the incident radiation and the surface
plasmon are matched. This does not occur under normal
circumstances, since the surface plasmon momentum is
5 always less than that of light. However momentum
matching can be achieved by a number of techniques:
- 10 i) Metal coated Prism ATR (attenuated total internal
reflection), also known as Otto or Kretschmann
geometry configuration as shown in Figures 2a and
2b. At a particular angle of incidence, the
momentum of the evanescent wave matches the
surface plasmon mode ensuring efficient surface
plasmon generation.
- 15 ii) Use of a metal coated grating to ensure momentum
matching (Figure 2c). The wavelength and angle of
incidence of the illumination source and the
grating pitch, depth and groove shape are chosen
to ensure efficient surface plasmon generation at
the interface. Illumination from the dielectric
20 side of the grating is possible if the metal
coating is sufficiently thin (< 10' nm) to allow
penetration of the enhanced electric field into
the material to be sensed.
- 25 iii) It is known that under optimised conditions of
physical parameters efficient surface plasmon
generation can occur when a colloidal suspension
of metalised spheres is illuminated. The
dimensions of the spheres should be comparable
with the wavelength of light. Figure 5
30 illustrates this arrangement, where the metal
coated spheres 9 are located in a housing which
constitutes the sensor head 1.
- 35 iv) Surface plasmon generation can also occur at a
statistically rough metal-dielectric interface.
We now describe ways in which some of these
geometries could be integrated with a catheter based
delivery system for in vivo blood gas analysis.

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- 1 Unique features of this sensor are as follows.
- 5 A sub-miniature system allowing delivery of the complete sensor into the blood supply, remote from the illumination source and detection systems.
- 10 Intregration of the light delivery and collection systems (fibres) and the interaction surface. For example:
- 15 i) As shown in Fig. 6, the end of the fibre 5 may be metal coated as at 11. Dielectric cladding 10 surrounds the fibre 5. A gas-permeable membrane 12 overlies the metal layer 11. Surface plasmon generation can then occur in a similar way to the Kretchmann geometry of Figure 2a. Here "free space" propagation of the conventional Kretchmann arrangement is replaced by a coupling of a propagation mode of the fibre to the surface plasmon mode. Raman scattered light can be collected by the same fibre.
- 20 ii) Minaturised and integrated fibre grating assemblies are shown in Figure 7. A spherical collimating lens 13 is attached to the end of the fibre 5 which provides illumination and a combined membrane/grating support 14 is provided between the lens 13 and a grating 15. Alternatively, a fibre structure could be moulded into the fibre tip and metallised, as at 15 in Figure 8.
- 25 iii) An arrangement utilising a colloidal suspension of metal spheres is shown in Figure 9.
- 30 In all the described configurations, it is essential that the sensor areas be surrounded by a membrane structure (indicated as either 12 or 14) permitting the flow of blood gases into the sensor volume but preventing the sensor from coming into direct contact with the blood. The total diameter of the sensor should
- 35 not exceed 2 mm.

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1 Claims:

1. Apparatus for sensing blood gas concentration in vivo, which comprises a probe adapted for emplacement 5 in a vein or artery and including: (a) at one end thereof, a gas-permeable membrane formed of a biologically acceptable material; (b) contiguous with said membrane, an active surface in the form of a surface capable of supporting a plasmon resonance; and (c) a 10 light guide of a type capable of transmitting a light input to said active surface and of transmitting a light output away from said active surface, without mutual interference, wherein the light guide constitutes a support or substrate for said active surface and is in 15 optical communication therewith.

2. Apparatus as claimed in claim 1, wherein said light guide comprises a pair of optical fibres, one functioning as an afferent light guide and the other functioning as an efferent light guide.

20 3. Apparatus as claimed in claim 1 or 2, wherein said surface is a grating.

4. Apparatus as claimed in claim 1 or 2, wherein said surface is a metal coated fibre.

25 5. Apparatus as claimed in claim 1 or 2, wherein said surface is a suspension of metal particles whose dimensions are of the order of the wavelength of light.

6. Apparatus as claimed in claim 1 or 2, wherein said surface is a statistically rough surface.

30 7. Apparatus as claimed in claim 1 or 2, wherein said surface is a prism one surface of which is coated with a thin film of a metal.

8. Apparatus as claimed in any preceding claim, wherein said active surface, said gas-permeable membrane and said light guide are housed in a catheter.

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- 1 9. Apparatus as claimed in claim 8, which further comprises a source of coherent light located remote from said active surface but optically in communication therewith via said light guide.

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Fig. 1.

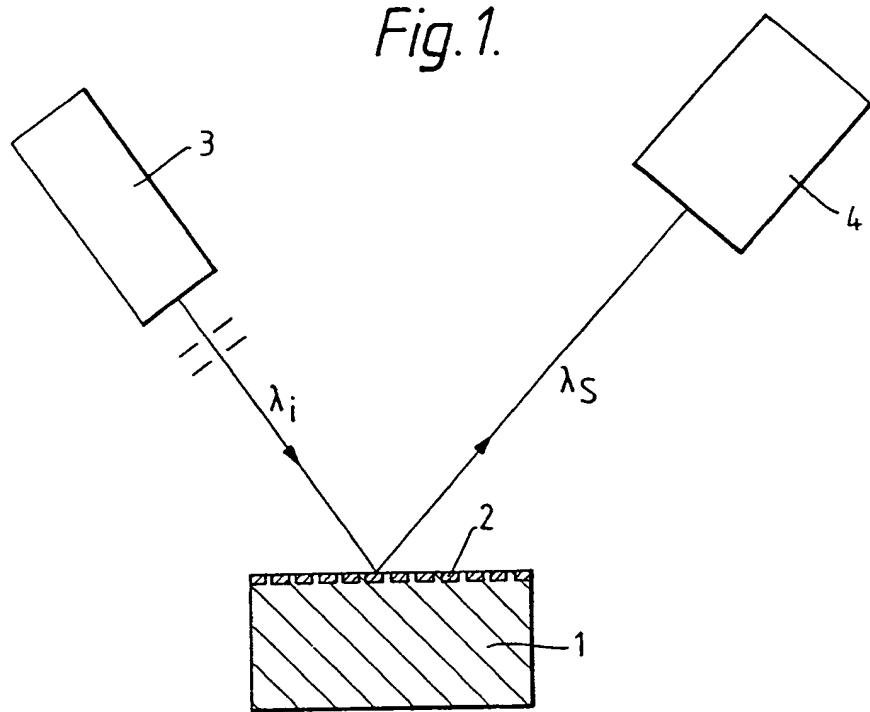


Fig. 2a.

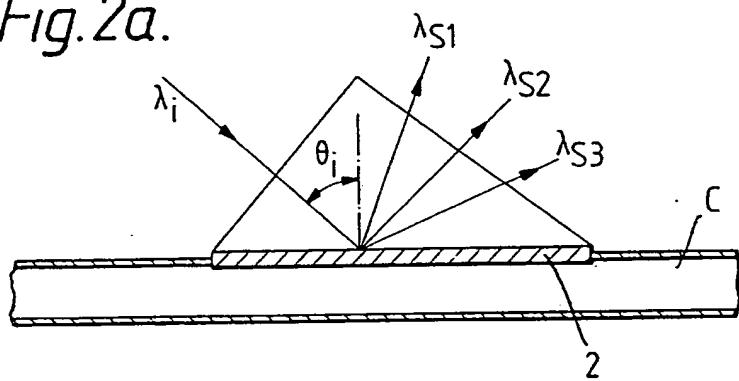
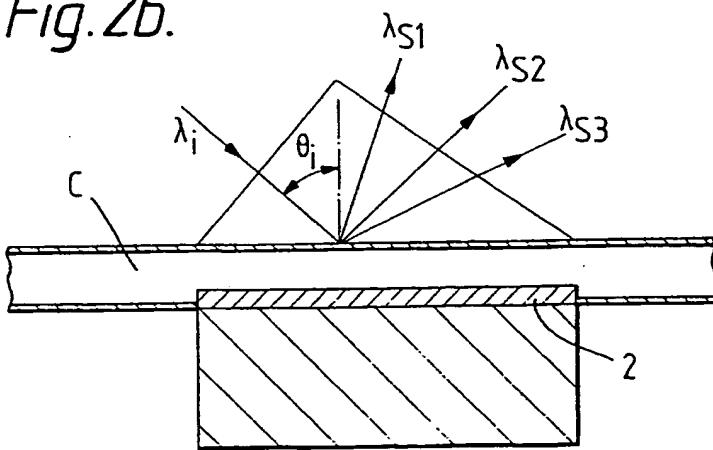


Fig. 2b.



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Fig. 2c.

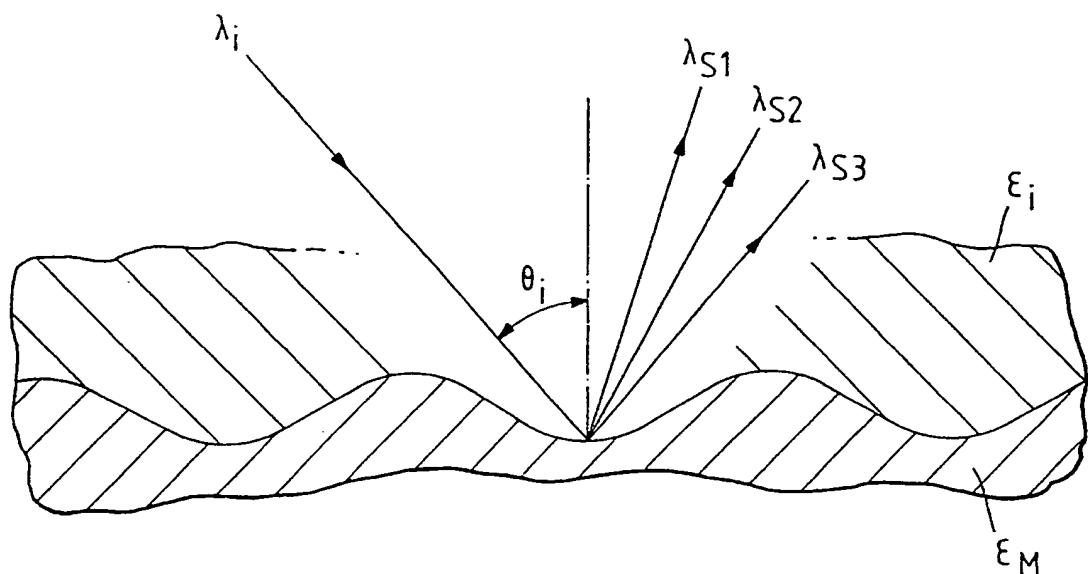


Fig. 3.

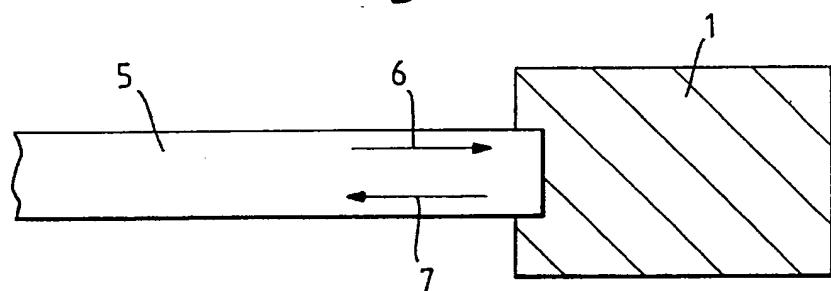
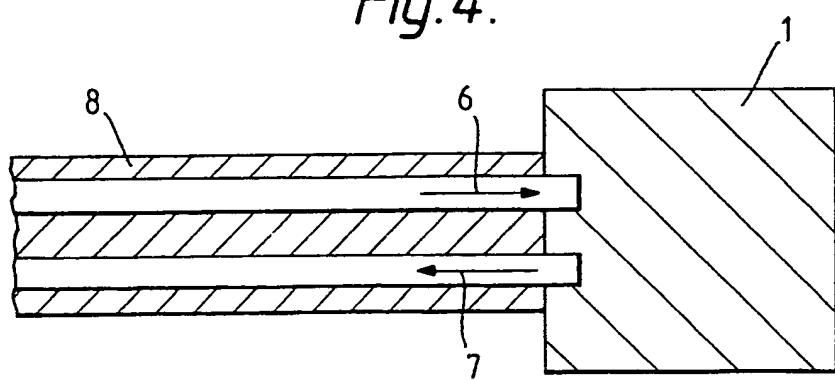
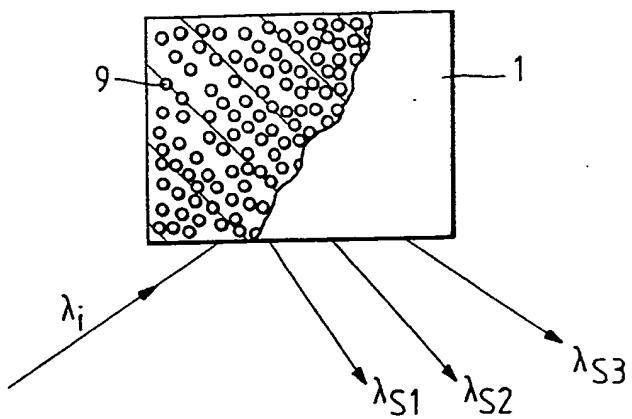
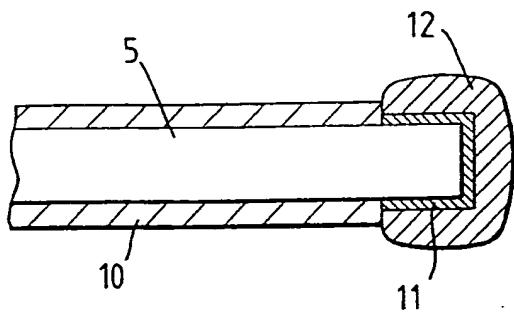
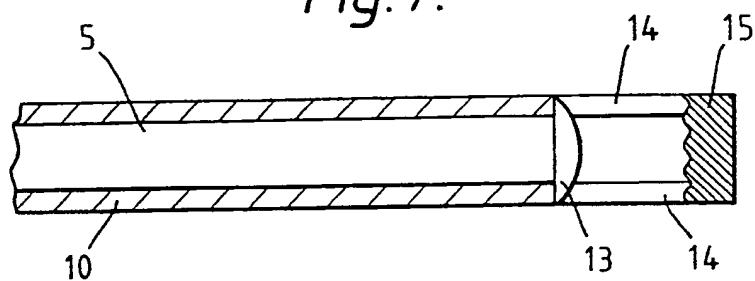
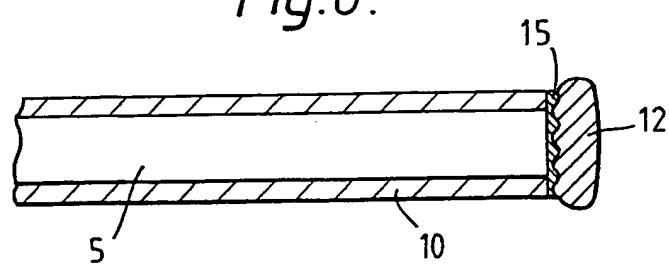
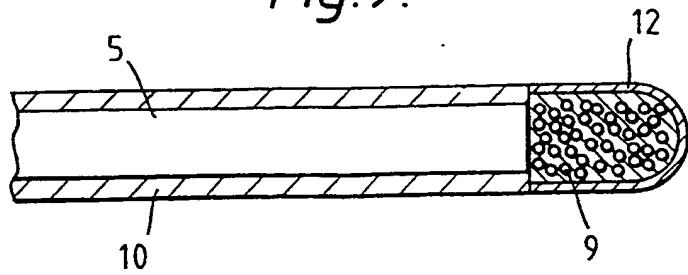


Fig. 4.



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Fig. 5.*Fig. 6.**Fig. 7.**Fig. 8.**Fig. 9.*

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 88/00125

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: G 01 N 21/65; A 61 B 5/00

II. FIELDS SEARCHED

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IPC ⁴	A 61 B 5/00; G 01 N 21/55; G 01 N 21/17; G 01 N 21/77; G 01 N 21/65

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III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	Analytical Chemistry, volume 54, no. 9, August 1982, American Chemical Society, (US), I. Chabay: "Optical waveguides", pages 1071 A - 1080 A see page 1074 A, left-hand column, "This protruding field", middle and right-hand column; page 1077 A, paragraphs 1,2	1,2,7
A	IBM Technical Disclosure Bulletin, volume 23, no. 11, April 1981, (New York, US), J.G. Gordon et al.: "Use of gratings to detect small quantities of materials by raman spectroscopy", page 5099 see the whole article	1,3
A	GB, A, 2173895 (PLESSEY CO.) 22 October 1986 see page 1, lines 44-61	3,5,7
A	IEEE Transactions on Biomedical Engineering, volume BME-33, no. 2, February 1986, IEEE, (New York, US),	1,2,8,9

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IV. CERTIFICATION

Date of the Actual Completion of the International Search

2nd June 1988

Date of Mailing of this International Search Report

- 5 JUL 1988

International Searching Authority

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Signature of Authorized Officer

P.C.G. VAN DER PUTTEN

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	<p>J.L. Gehrich et al.: "Optical fluorescence and its application to an intravascular blood gas monitoring system", pages 117-132 see pages 118-120, "Blood gas probe design"; pages 121-122, "Optical pO₂ sensor" and "Instrument design"</p> <p>-----</p>	

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 8800125
SA 20932

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2173895	22-10-86	EP-A- 0202021 JP-A- 61292045	20-11-86 22-12-86

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